Background: CD19-targeted chimeric antigen receptor (CAR) T cell therapy has demonstrated remarkable clinical efficacy in treating relapsed/refractory B-cell acute lymphoblastic leukemia (ALL). However, there are potential treatment-related toxicities, which may be severe. Acute kidney injury (AKI) has been reported after CD19 CAR T cells, but not systematically evaluated. We sought to describe AKI incidence, severity, outcome, and risk factors in the first 30 days after CTL019, a CD19 CAR T cell therapy, for ALL in pediatric patients.

Methods: We studied patients treated with CTL019 through two clinical trials (NCT01626495 and NCT02906371) at Children’s Hospital of Philadelphia between April 2012 and April 2018. Demographic, laboratory and pharmacy data were automatically extracted from the electronic medical record using an EPIC data query tool. The primary outcome was AKI within 30 days after CTL019 infusion. AKI was defined using the Kidney Disease: Improving Global Outcomes criteria. Stage 1 (serum creatinine (SCr) ≤ 1.5 times the baseline) was classified as mild AKI. Stage 2 or 3 (SCr >2 times the baseline) were classified as severe AKI. Renal recovery was defined as improvement in SCr to within 1.5 times the baseline by day +30. Log-binomial regression was used to estimate risk ratios for the association of cytokine release syndrome (CRS) and severe AKI. Additional analyses will compare the trajectories of CRS biomarkers and tumor lysis labs with the trajectory of AKI in order to better elucidate mechanisms of renal injury and identify opportunities for intervention.

Conclusion: In the first 30 days after CTL019 infusion, 21% of patients developed AKI, but most recovered renal function by day +30. AKI was strongly associated with Grades 3 and 4 CRS and developed at a median of 5 days after the start of CRS. Additional analyses will compare the trajectories of CRS biomarkers and tumor lysis labs with the trajectory of AKI in order to better elucidate mechanisms of renal injury and identify opportunities for intervention.

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CD19 Directed Chimeric Antigen Receptor T Cell Therapy in Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis

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Introduction: Chimeric antigen receptor (CAR) T-cells targeting CD19 have led to complete response (CR) rates of 70-90% in children and adults with refractory/relapsed B-cell acute lymphoblastic leukemia (ALL), which led to their FDA approval in 2017. However, different constructs have been used and the response rates vary among different studies. Toxicities in the form of cytokine release syndrome (CRS) and neurotoxicity remain a challenge. We conducted a systematic review and meta-analysis of all published and presented trials of anti-CD19 CAR T-cells in relapsed/refractory ALL.

Objectives: 1) To determine the efficacy of anti-CD19 CAR T-cells in ALL. 2) To describe the toxicities of anti-CD19 CAR T-cells in ALL. 3) To examine differences in efficacy and toxicity by age groups and construct type.

Methods: We searched MEDLINE and EMBASE and included studies that reported raw data on the outcomes of adults and children that were treated with anti-CD19 CAR T-cells for ALL. The random effects model was used to derive estimates of complete response (CR) and progression-free survival (PFS) at 1 year and toxicities. Secondary outcome was minimal residual disease (MRD) at 1 year. We planned subgroup analysis based on age (adults vs. children) and construct type.

Results: Of 1,139 potentially relevant references, 18 noncomparative trials were included with a total of 573 patients (309 adults and 264 children). Pooled CR was comparable between adults [84% (95% CI 80-86%)] and children [83% (95% CI 79-88%)], but varied by construct [86% (95% CI 82-90%) for 41BB co-stimulated CART cells vs 74% (95% CI 68-81%) for CD28 co-stimulated CART cells vs 86% (95% CI 80-91%) for fourth-generation CART cells]. Pooled 1-year PFS was comparable for adults and children [35% (95% CI 31-74%) vs 56% (95% CI 50-65%)]. CRS rates were comparable among adults and children [76% (95% CI 71-81%) vs 72% (95% CI 68-77%)]. CRS was lower in CD28 compared to other constructs [47% (95% CI 41-53%) in CD28 vs 86% (95% CI 82-91%) in 41BB vs 76% (95% CI 69-83%) in fourth generation]. Neurotoxicity occurred more commonly in adults recovered renal function by day +30. Patients with Grade 3/4 CRS had a 4.9 times greater risk of developing AKI (95% CI, 2.4 to 9.9; p<.001) and a 10.3 times greater risk of developing severe AKI (95% CI 3.1 to 34.3; p<.001) than patients with no or Grade 1/2 CRS (Figure 1). The median time to CRS start, AKI onset, and maximum SCr level were 2, 7 and 9 days after infusion, respectively. History of hematopoietic cell transplant prior to CTL019 was not significantly associated with AKI, nor were age, sex, race, and ethnicity.

[44% (95 CI 35-54%) vs 17% (95 CI 12-22%)] and in those treated with 41BB compared to those treated with CD28 [34% (95 CI 27-40%) vs 14% (95 CI 9-20%)]. Pooled MRD negativity at 1 year was 77% (95 CI 71-82%) in adults and 82% (95 CI 77-87%) in children. CD28 construct led to lower MRD negativity [62% (95 CI 54-70%) vs 85% (95 CI 81-89%) in 41BB vs 81% (95 CI 69-93%) in fourth generation]. These data are summarized in Figure 1.

Conclusions: Pooled 1-year CR was 84%, pooled 1-year PFS was 57% and the efficacy of CAR T-cell therapy was comparable between adults and children. Analysis by construct type revealed differences in the efficacy and toxicity between different constructs with CD28 leading to lower efficacy and toxicity. This is the first study to systemically analyze the outcomes of anti-CD19 CAR T-cell therapy in ALL.

Figure 1. (A) Forest plots of 1-year CR and PFS rates by age. 1-adults, 2-children. (B) Forest plots of CR and PFS rates at 1 year by construct. 1-41BB, 2-CD28, 3-fourth generation. (C) Rates of CRS and neurotoxicity at 1 year by age. 1-adults, 2-children. (D) Rates of CRS and neurotoxicity by construct. 1-41BB, 2-CD28, 3-fourth generation.

Methods: Pediatric/young adults with R/R B-ALL were eligible for infusion. Patients received cyclophosphamide-based (Cy) conditioning of high dose (HD; 3g/m²) or low dose (LD; 1.5g/m²) chemotherapy. Outcomes of interest were complete response (CR) and overall survival (OS). Variables considered were conditioning regimen (HD vs LD), pre-treatment disease burden (MRD vs morphologic), complete remission (CR) status, absolute lymphocyte count (ALC) change, and in vivo CAR T cell expansion.

Results: 25 pts were included; 17 pts received HD-Cy and 8 pts received LD-Cy prior to CAR T cells. Among evaluable pts (n=24), CR/CRI was demonstrated in 94% and 38% for HD-Cy vs LD-Cy cohorts respectively (p=0.01). OS was superior in the HD-Cy cohort as compared to the LD-Cy cohort (median OS not reached; NR) vs. 44 months (p=0.004; Figure 1). Lymphodepletion (Delta ALC: prior/following Cy) was higher in the HD-Cy cohort as compared to the LD-Cy cohort (p=0.001; Figure 2). The in vivo CAR T cell expansion (peak CAR T cell vector copy number/ ml) in peripheral blood was higher in the HD-Cy cohort as compared to the LD-Cy cohort (p=0.01; Figure 2). To less extent, disease burden prior to treatment with conditioning chemotherapy and CAR T cells impacted response. Disease response was 93% (13/14) in low disease burden group (MRD-cohort) compared to 50% (5/10) in the high disease burden group (morphologic cohort) (p=0.05). OS was also superior in the low disease burden group (median OS = NR) compared to high disease burden group (median OS = 4.3 months; p=0.01). Combined response for HD-Cy/MRD was 100% (12/12), HD-Cy/Morphologic 75% (3/4) LD-Cy/MRD 50% (1/2), and LD-Cy/Morphologic 33% (2/6). Grade III/IV toxicity occurred in 32% (8/25) of pts including severe cytokine release syndrome (sCRS) in 16% of pts and severe CAR-associated neurotoxicity in 28% of pts.

Findings: In this preliminary analysis we demonstrate that dose intensity of conditioning chemotherapy positively correlated with CR and OS for pts treated with CAR T cells and confirms, to a lesser extent, pre-treatment disease burden impacts both CR and OS.

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Conditioning Prior to CAR T Cells Predicts Response and Survival in Pediatric/Young Adult Relapse/Refractory (R/R) B-ALL

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Introduction: CD19-specific CAR T cells have clinical benefit in patients (pts) with R/R B-ALL. Several factors have been associated with response: conditioning chemotherapy, CD4/8 ratio, and post-infusion CAR T cell expansion.


Figure 1. OS for pts with R/R B-ALL who received 19-28z CAR T cells based on cohort – 83% of responding patients underwent consolidation with allo-HSCT.

Figure 2. (A) ALC prior/following Cy (ALC change; n=23) and was higher in the HD-Cy compared to the LD-Cy cohort (p<0.001; Figure 2). (B) in vivo CAR T cell expansion in peripheral blood was higher in the HD-Cy compared to the LD-Cy cohort (p=0.01).